of a vector for delivery of a virus comprising said therapeutic agent to a target cell within said animal, said vector comprising a cell-targeting ligand non-covalently bound directly to said virus and said target cell containing a receptor for said ligand.

Claim 30 (amended). The method of claim 19, wherein said virus is comprised of a nucleic acid encoding wild-type p53, further wherein said cell-targeting ligand is transferrin and said therapeutic agent is administered systemically.

REMARKS

Support for the amendment to page 6 of the specification can be found in Example 9 of the application.

The application was objected to as having several informalities. The examiner asserted that the title of the description was not sufficiently descriptive and suggested a new title. Applicants have amended the application above to replace the original title with a modification of the one suggested by the examiner. The examiner also objected to the application on the basis that it does not contain an abstract. This objection has been obviated by the provision of an abstract, above. Finally, the examiner also objected to the description of the drawings for Figure 6 because there was no indication of what "TxT" stands for. This objection has been obviated by the amendment to the description of Figure 6, above.

Claims 1-11 and 13-32 have been rejected under 35 U.S.C. § 112, first paragraph, on the basis that the specification, although enabling for a vector comprising a transferrin non-covalently bound directly to a virus for delivery to a target cell containing a transferrin receptor, does not provide enablement for an invention commensurate in scope with the scope of the claims. The examiner asserted, in part, that the claims

are too broad because, although some of the claims broadly recite "a virus," the specification only provides evidence of mixing transferrin with three types of viruses--adenoviruses, retroviruses, and Herpes simplex virus--for vector preparation and delivery to target cells. He also asserted that there is no guidance as to how ligands other than transferrin could be mixed with any virus to produce a vector that will deliver a transgene encoded by the virus to specific targeting cells. This rejection is traversed.

As the examiner noted, Applicants have illustrated their invention using three different viruses--an adenovirus, a retrovirus and a Herpes simplex virus. These are three very different types of viruses, having different sizes and mechanisms of action. These viruses are representative of three broad classes of viruses: Adenoviruses represent small, non-enveloped, double-stranded DNA viruses, 70-80 nm in diameter; retroviruses carry RNA, rather than DNA, as their genome along with the mechanism for transcribing DNA from RNA; and Herpes simplex virus is representative of the class of Herpetoviridae, which are large, enveloped, DNA viruses with an overall diameter of 150 nm. Thus, these three examples exemplify the size range, type of genome and coating (presence or absence of an envelope) evident in the great majority of known viruses and are representative of many other viruses in the same family and/or classification. Given the demonstrated efficacy of the invention with each of these three viruses, it is reasonable and appropriate to conclude that vectors comprising other types of viruses also can be constructed and used to provide a therapeutic agent to a patient suffering from cancer of the head and neck, bladder, breast, thyroid, ovary or prostate, or from a melanoma or a lymphoma.

With regard to the examiner's concern regarding the lack of evidence that ligands other than transferrin stably can bind non-covalently to a given virus and deliver a transgene *in vivo* to a target cell, Applicants submit herewith a declaration by co-inventor Esther Chang which summarizes the results obtained in experiments in which an antibody fragment or EGF was used as the cell targeting ligand. As is clear from this declaration, the results obtained from these experiments demonstrate that molecules other than transferrin also can covalently, directly complex viruses and enhance virus gene transduction.

With regard to the cell-targeting ligand, it is noted that the examiner expressed concern on page 6 of the Action that in the examples in the application different transferrin/virion ratios were used for vector preparation depending upon whether the vector was being used for *in vitro* transgene delivery or *in vivo* transgene delivery and that the ratios also varied depending upon the type of virus used. He asserted that in view of this, it would require undue experimentation to find the best ligand/virion mixing ratio. Applicants respectfully submit that one skilled in the art would not find the determination of a desirable ratio of ligand/virion to be undue experimentation. It is well-known in the art that the amount of a therapeutic agent useful to obtain a desired result often will vary when one moves from *in vitro* cell culture initial trials to *in vivo* administration. It also is well-understood that the optimal amount also can vary depending upon the type of virus, as the size, coat, and presence or absence of an envelope affect the specific optimal amount. Thus, the three different types of viruses exemplified by the Applicants provide guidance for the use of other viruses having a wide range of characteristics. Applicants have provided clear guidance on appropriate ranges of

useful concentrations; it would be a matter of simple routine for one of skill in the art to determine an optimal concentration for a particular vector of interest in view of these teachings. The fact that a test or procedure may need to be repeated to determine an optimal amount or concentration does not make the experimentation "undue:"

> The test [for undue experimentation] is not merely quantitative, since a considerable amount of experimentation is permissible, if it is merely routine, or if the specification provides a reasonable amount of guidance with respect to the direction in which the experimentation should proceed to enable the determination of how to practice a desired embodiment of the claimed invention.

Ex parte Forman 230 USPQ 546; 547 (B.P.A.I. 1986).

With regard to claims 19-32, the examiner noted that the specification only provides evidence of *in vivo* efficacy of the invention with regard to an adenoviral vector encoding p53 targeting a target cell in an SCCHN Xenograft nude mouse or to a target cell in an immune competent B_{16} mouse with melanoma lung metastases. He asserted that as there was no evidence as to delivery of a therapeutically effective amount of the same vector to cancer cells in a non-mouse patient, nor to other types of cancer cells and that, therefore, the claims were not enabled. He noted that cancer is a complex disease and that the specification does not provide any guidance as to which types of cancer can be treated, or at what step in cancer development the cancer can be treated or what transgene can be used. He further asserted that mouse models are not satisfactory models for studying many human disorders, including cancer, and that, therefore, human studies are necessary to develop effective treatments. This rejection is traversed.

The picture painted by the examiner of the difficulties of developing effective cancer treatments was painted with an overly broad brush. As an initial point, Applicants wish to point out that the focus of their invention is not the development of new agents effective as anti-cancer agents *per se*; the focus of the invention is on improvements in getting therapeutic agents, such as anti-cancer agents, to cancer cells. The invention provides compositions and methods for targeted delivery of established therapeutic nucleic acids to a specific organ, tissue or tumor. The background section of the specification describes the advantages--and disadvantages--of the use of viral vectors to date to transfer nucleic acids into host cells. One of the most significant problems has been how to target viral particles to specific cell types. Applicants have solved this problem through their development of a delivery system comprising a virus, containing a nucleic acid encoding a therapeutic agent, directly and non-covalently linked to a transferrin molecule. These vectors efficiently target tumor cells which contain a transferrin receptor.

It is well-known in the art, as Applicants point out on page 2 of their application, that the transferrin receptor is elevated on many tumor types. See, for example, Singh, M., *Curr Pharm Des* 5(6):443-451 (Jun, 1999) ("Transferring has been used as a ligand for delivering anticancer drugs or drug containing liposomes mostly due to the increased number of transferrin (trf) receptors found on tumor cells as compared to normal cells"); Thorstensen, K., and I. Romslo, *Scand. J. Clin Lab Invest* 53(Suppl. 215):113-120 (1993) ("Histochemical analysis of the presence and abundancy of the transferrin receptor will continue to serve as an additional tool in special cases to distinguish between malignant and normal cell growth"); and Yang, D.G. et al., *Anticancer Res.*,

21:1777-1788 (2001) ("tumor cells in a highly proliferative state have a high density of transferrin receptors"); copies of which are included herewith. And, contrary to the examiner's assertion, Applicants have provided guidance as to cancer types in which tumor cells are characterized as containing a transferrin receptor. Accordingly, persons of skill in the art are provided with clear guidance on cancer types which can be treated through the administration of a vector in accordance with the present invention.

As for the examiner's contention that there is no guidance as to what stage of cancer is appropriate for treatment using the compositions of this invention, Applicants respectfully submit that there is no need for such a determination. A cancer cell that contains a transferrin receptor contains that receptor whether the cancer is in an early stage of development or is highly advanced. Similarly, an agent which is therapeutic, such as the tumor suppressor gene p53, can be administered advantageously regardless of whether a patient's cancer is caught early on or at an advanced stage. See, for example, Selivanova, G., *Current opinion in Investigational Drugs* 2(8):1136-1141 (2001) ("Alterations in the p53 gene are the most common genetic defects found in tumors so far. Taking into account that p53 is a powerful inducer of cell death it is not surprising that the abolition of its function occurs almost universally during tumor development.") and Zeimet, A. et al., *Biochem. Pharm.* 60:1153-1163 (2000); copies of which are included herewith. The key is having an efficient way of getting the virus comprising the therapeutic agent to the tumor cell and achieving high levels of infectivity, so that the therapeutic agent can be effective, and that is what is accomplished by the present invention.

As noted above, the examiner also asserted that because the *in vivo* data presented in the application were obtained from mice, the application did not enable the administration to humans, because mice are not an effective model for cancer treatment in humans. Again, Applicants respectfully submit that this statement is over-reaching and, therefore, inaccurate. The examiner appears to have overlooked that although the *in vivo* experiments were carried out in mice, in all but Example 7 the mice were ones in which xenografts, i.e., human tumors, had been induced. The use of xenograft-induced mice is, in fact, the standard model in the field of cancer treatment. Applicants respectfully direct the examiner's attention to the website for the National Cancer Institute, an entire section of which focuses on mouse models. The NCI has a collaborative program, the NCI Mouse Models of Human Cancers Consortium (MMHCC), and sponsors a variety of other projects to "Develop, analyze and apply mouse cancer models." See the first page of the "emouse" portion of the NCI web site, a copy of which is attached. Also attached is the first page of the "Mouse Models" subsection of that portion of the site.

The sole exception to the use of xenografts in the Examples portion of the current application is in Example 7, in which the model was mice with mouse melanoma lung metastases. This model also is well-established and is important in that the mice are not athymic nude mice but are fully immune competent animals and, therefore, even more closely approximate human patients. Thus, this example demonstrates that the presence of an intact immune system is not a hindrance to the therapeutic value of this invention.

Accordingly, Applicants respectfully submit that the claims pending in this application are enabled and fully meet the

requirements of the first paragraph of §112 of the patent statute. They have provided clear evidence that a recombinant virus, which comprises a therapeutic nucleic acid and is directly and noncovalently coupled to a transferrin molecule, can be administered to a patient to target cells, such as tumor cells, which contain a transferrin receptor, to achieve a high level of infectivity and targeted delivery of the contents of the viral particle. The data in the Examples indicate that Tf-virus complexes are capable of producing significantly higher levels of gene expression in tumors than that seen with untargeted vectors. Further, data illustrate that the administration of Tf-virus complexes comprising a therapeutic nucleic acid results in the inhibition of tumor growth. In one embodiment of the invention, the vectors are administered in combination with conventional radiation or chemotherapy, and resulted in not only tumor growth inhibition but tumor regression, and demonstrated a synergistic effect. Given the known adverse side effects associated with high doses of either radiation or chemotherapy, a method by which tumors could be sensitized so as to allow a lower effective dose of the conventional treatment provides enormous clinical benefit.

Claims 1-4, 6-10 and 19-24 have been rejected under 35 U.S.C. § 102(e) as anticipated by U.S. Patent 5,962,311, issued to Wickham et al. (hereinafter referred to as the '311 patent). The examiner characterized the patent as teaching a recombinant virus comprising a short-shafted fiber to increase the specificity of binding of the virus to a given cell by direct or indirect binding and a method of targeting the recombinant virus to a cell by contacting the virus vector with a bispecific or multispecific binding agent that selectively binds by non-covalent interaction. This rejection is traversed.

As the examiner noted, the '311 patent teaches making a recombinant virus wherein the virus comprises a non-native gene and a short-shafted fiber. The short-shafted fiber is a required element of the recombinant virus and the means by which the virus attaches to a target cell. The patent does not teach or suggest noncovalently and directly binding a transferrin molecule to a virus or that a virus, containing a therapeutic nucleic acid, to which a transferrin molecule has been so bound can be delivered, *in vitro* or *in vivo* to a target cell containing a transferrin receptor such that the therapeutic nucleic acid is expressed within the target cell. As there is no teaching or suggestion in the '311 patent of a key element of the presently claimed invention, the reference does not anticipate the claims.

Claims 5, 25 and 27-29 were rejected under 35 U.S.C. §103(a) as obvious over the '311 patent cited above in view of U.S. Patent 6,410,010, issued to Zhang et al. (hereinafter referred to as the '010 patent). The examiner asserted that although the '311 patent does not teach using a viral vector to encode the p53 tumor suppressor gene, the '010 patent teaches using adenovirus encoding p53 for gene therapy for cancer cells with aberrant p53 functions. The examiner asserted that it thus would have been prima facie obvious to one of ordinary skill in the art to use a vector in accordance with the '311 patent to deliver the p53 gene for gene therapy for cancer cells with aberrant p53 functions given the teachings of the '010 patent. This rejection is traversed.

The shortcomings of the '311 patent described above are equally applicable to the present rejection. The patent does not teach or suggest noncovalently and directly binding a transferrin molecule to a recombinant virus. This critical shortcoming of the primary reference is neither taught nor suggested by the

cited secondary reference. Accordingly, even if one were to assume, for the sake of argument, that one of ordinary skill in the art familiar with both references would insert a p53 gene into the adenovirus of the '311 patent, one would not arrive at the present invention, as the resultant recombinant virus would not comprise a transferrin molecule noncovalently and directly bound to the virus and the recombinant virus would not target cells containing a transferrin receptor.

In view of the foregoing amendments and arguments, Applicants respectfully submit that the claims pending in this application are in condition for allowance.

☒ Customer Number or Bar Code Label **6449**					
Name	Barbara G. Ernst, Reg. No. 30,377				
Signature	Barbara G. Ernst			*Date*	Dec. 10, 2002
Address	Rothwell, Figg, Ernst & Manbeck Suite 800, 1425 K Street, N.W.				
City	Washington	*State*	D.C.	*Zip Code*	20005
Country	U.S.A.	*Telephone*	202-783-6040	*Fax*	202-783-6031

Attachment: Marked up copy of amendments

Marked Up Copy of Title

~~Systemic Viral/Ligand Gene Delivery System and Gene Therapy~~Ligand-Mediated Viral Delivery System for Gene Therapy

Marked Up Copy of Amended Portions of the Specification:

Page 6, 3rd paragraph should read:

Figure 6. Effect of the combination of systemically delivered, tumor-targeted adenoviral-p53 and chemotherapy (Taxotere® (TxT)) on MDA-MB-435 xenograft tumors *in vivo*.

Marked Up Copy of Amended Claims:

Claim 1 (amended). A vector for delivery of a virus to a target cell within a host animal, comprising a cell-targeting ligand non-covalently bound directly to said virus.

Claim 17 (twice amended). A method for preparing a vector for the systemic delivery of a virus to a target cell, said vector comprising a cell-targeting ligand non-covalently bound directly to said virus, comprising mixing said cell-targeting ligand with said virus in an aqueous medium, whereby said ligand non-covalently binds directly to said virus.

Claim 19 (amended). A method for providing a nucleic acid therapeutic agent to an animal suffering from head and neck cancer, bladder cancer, breast cancer, thyroid cancer, ovarian cancer, prostate cancer, melanoma or lymphoma ~~in need thereof~~, comprising administering to said animal a therapeutically effective amount of a vector for delivery of a virus comprising said therapeutic agent to a target cell within said animal, said vector comprising a cell-targeting ligand non-covalently bound

directly to said virus and said target cell containing a receptor for said ligand.

Claim 30 (amended). The method of claim 19, wherein said virus is comprised of a nucleic acid encoding wild-type p53, further wherein said cell-targeting ligand is transferrin and ~~further whereby~~ said therapeutic agent is administered systemically.